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DISEASES OF THE NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

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DISEASES of the NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Inspiration and Method in Schizophrenia Research

HUMPHRY OSMOND, M.R.C.S., D.P.M.
Regina, Saskatchewan

As an amateur and a clinician I am unqualified to offer an opinion on many of the subjects which I shall discuss. However, sometimes the unspecialized eye is more useful than the microscopic or the telescopic. My colleagues whose skills range from the physio-chemical to the philosophical, must for the present be guided by the unspecialized psychiatrist in a wood where the trees grow as thick as in schizophrenia. One day I believe things will be very different and because I am hopeful that this will be so within the lifetime of many of us, I am going to have my say before the specialists are well enough established to contradict me.

If I offend some, by an orotund phrase or by turning a quotation where it would seem that exact description would be better, forgive me. This is an essay in communication and must risk failure when one is attempting to describe experiences and research on experiences which many consider incommunicable.[7,10,15,29,32,33,36,41,43,45,52]

What can we do? Would it have been truthful or wise to describe the explosion of an atomic bomb in 1945 as "a somewhat larger bomb than usual"? Understatement can be as absurd as exaggeration. Some of the events which I shall touch on are, according to those who have endured them as astonishing and unlikely as those discoveries in nuclear physics which we have learned to bear with simulated equanimity.

If we are scientists we must bow to brute facts whether these occur in physics or psychiatry.

Lines of Attack:

There seem to be three paths which lead to that adventure in discovering the relationships between phenomena which we call research. These paths are sometimes superimposed and sometimes diverge so far that they do not seem to be going in the same direction.

A. The Concrete or Empirical Method:

These are the fact finders or even fact hoarders. There are many famous names here and I shall only mention a few in passing. But remember there is no pure empiricist for even the most assiduous, believes that the facts which he collects are in some way related to one another. Though it is often not admitted there must be some hidden core of theory, for without it there could be no selection. Hoskins,[28] Gjessing[19] and Weil Malherbe[58] are great names among empiricists in schizophrenia research, although they are rarely explicit about it. The most straightforward statement of empiricism, of fact worship, which I have read, was made by one of the notable exponents of this method recently at the Magdalen Symposium in Oxford, March, 1952. He is commenting on a plea for better co-operation between

Presented at the American Psychiatric Association Regional Research Meeting at McGill University, 4th December, 1953.

Written under the auspices of the Saskatchewan Committee for Schizophrenia Research, supported by the Department of National Health and Welfare, Canada.

the sciences bordering on psychiatry and he says:

"It has been mentioned from time to time that we need more integration, more thought behind research. I believe that what we need most of all is more facts, and I believe that when we have enough facts the thoughts will take care of themselves. That is not a thing which we should primarily worry about. The ignorance about the fundamental problems in psychiatry is so great that there is enough to do for all types of research workers and though at present the facts may seem like a jig-saw puzzle, when we have enough of them they will fall into place."[58]

Surely this is idolatry.

This able man could not have chosen a better metaphor to illustrate the weakness of what he advocates. Indefinite multiplication of the pieces of a jig-saw puzzle is no help in solving it, but simply increases the size of the jumbled heap. There is something nightmarish in the thought of the scientist ceaselessly gathering facts in the mistaken belief that they are falling into place, when, in reality, they are begetting confusion.

B. The Users of Systematic Theory:

Opposed to the empiricists are the systematic Theorists, who instead of depending upon an accumulation of facts to produce an answer to their questions by spontaneous generation, trim the facts with procrustean zeal to fit their system. They often omit to produce testable hypotheses.

The history of science abounds with great systematic mausoleums, whose magnificence so bemused whole centuries of seekers that they could not see that there were only corpses inside. The wonderful theory of the celestial spheres[12] survived observations which to our way of thinking made it untenable. The phlogiston theory kept its appeal long after enough evidence had accumulated to make nonsense of it. The humoral theory dominated medicine for generations. Great systems often impede discovery because they become so venerated that no one questions their basic assumptions. For hundreds of years people were bled and purged and clystered to death because according to the humoral theory this would make them well. Despite the weak and exsanguinated patients who died in front of their eyes, doctors continued to impose their system on the facts. There was a ready answer: those who did not respond to bleeding needed only further bleeding to save them. And so they died on the altar of systematic theory.

In schizophrenia research there have been at least two attempts to use general theories to account for this great insanity, which have received some support from psychiatrists. The Freudians have made attempts to include it in the formulations of psychoanalysis. I do not think they have ever succeeded in convincing themselves that it could be entirely accounted for in psychological terms[50] and their views have never gained wide support from those who had to spend their time working among the victims of schizophrenia. The procrustean bed applied by the obduracy of the facts defied pruning.

More recently variations on Hans Selye's Theory of stress have been smuggled into psychiatry accompanied by hints that it would help us to understand schizophrenia. I shall not challenge the G. A. S. in Montreal, but I shall challenge those in Canada and Britain who attempt to foist it on psychiatry without indicating clearly what purpose is served by a system of this sort, which does not so far as I can discover, advance any testable hypothesis. I shall quote an example of this sort of theorizing which was produced at the Magdalen symposium and echoed by others present. In a recent Canadian publication[13] another distinguished researcher expresses, if I read him aright, a somewhat similar belief. The systematic Theorist speaks:

"Another is Selyes' idea of stress syndrome, which likewise helps us to put in order a great amount of biochemical facts and make them more relevant to our particular problem. I have a feeling that much of biochemistry would become relevant as more and more of these general principles are described and established and we should leave it until that occurs. For instance the problem of treatment by biochemical means must, I think, always be very difficult to justify, since the only thing that is quite clear from these various studies is that we are constantly dealing with complex interactions between relative variations of one enzyme system and another, so that the only possible biochemical treatment would be of the shot gun variety. In fact I think that transfusion of normal blood in abnormal persons is the only possible biochemical treatment."[47]

You may consider that this was in fact putting forward an hypothesis in the last sentence and not being rhetorical. Perhaps it was, but I have seen no reports that he has tested this hypothesis; although as it happens others have from time to time. No suggestion as to how these general principles are to be elucidated is offered.

System building which does not lead to hypotheses which can be tested has, in my view, no place in science. History suggests that its flashiness blinds us to the facts and hinders us from seeing them; and I have no doubt that it will do so in the future, if we abandon ourselves to the pursuit of this bauble.

To return to the jig-saw puzzle. While the empiricist labours to secure more and more pieces and never worries much about setting them out, the systematic theorist forces them together to make the picture which he knows must be there, regardless of whether they fit or not.

C. The Scientific Method:

The third method is no less exacting than empiricism and no less exciting than systematic theorizing. It differs from both because it approaches a goal by means of a number of planned steps. There are great advantages in making a hypothesis and testing it within a framework:

(1) The findings validate not only the specific hypothesis, but as the hypothesis itself is by definition framed within some established body of theory, they strengthen the theory which is itself of wider significance than the tested hypothesis. Building and testing hypotheses forces one to ponder the assumptions which have caused one to seek out certain facts and discard others. There is no such need to examine underlying assumptions inherent in "fact finding" itself; consequently extreme empiricism may easily lead, because of faulty assumptions, to great hoards of useless facts. Furthermore a "lost" hypothesis will force a re-examination of the whole research and this often results in fruitful redirection. In addition, the revision of any hypothesis must alter the general theory of which it is a part, and so the "lost" hypothesis may be as important as that which is sustained.

(2) General theory emerges not simply from a system of postulates, but after taking proper notice of the observed facts,[11,20] but how often has this been done in psychiatry? Speaking of our sister science Heinrich Klüver[34] has put the matter so well that I cannot do better than use his word, "And how is psychology to find the royal road to a deeper understanding of its unrelated series of observations? We see no other way except the one of penetrating experimental and theoretical analyses of *specific* problems, that is, the use of a procedure which has so often been successful in other sciences. . . . The theories and hypothesis of psychology, however, cover in general too great a range of phenomena and as a consequence become vague and superficial or else ignore the implications of specific phenomena and thus fail to reach true "generality." Claude Bernard rightly insisted 'Plus on descend dans l'intimité des phénomènes, plus on s'élève dans les généralités. Il ne faut pas confondre le superficiel avec le général.' We venture the prediction that a Copernican revolution initiating an era of rapid progress in psychology, if it ever occurs, will be brought about by the monographic treatment of *specific* problems and the detailed analysis of *particular phenomena.*"

I will not enlarge on the advantages of the scientific method. Round it has grown an elaborate instrument called methodology, which consists of a carefully codified series of rules of the scientific game. Methodology is becoming increasingly refined, and some of its expositors are so clamant that they might persuade novices that diligent attention to methodology alone is likely to bring success.

Herbert Dingle[12] himself a distinguished methodologist, has made the curious observation that we have no record of any great discovery which has ever been made by applying these rules, any more than great poetry has been written by studying verse forms. He writes: "Great thinkers are neither logical machines or magicians. We cannot follow the workings of their minds, but by studying what they did we can free ourselves from many misconceptions and perhaps catch some of the inspiration that made them what they were."

"This, I think, throws some light on the subject of 'scientific method' or 'methodology' as it is often called now. This is a discipline conducted for the most part by logicians unacquainted with the practice of science; and it consists mainly of a set of principles by which accepted conclusions can best be reached by those who already know them. When we compare these principles with the steps by which the discoveries were actually made we find scarcely a single instance in which there is the slightest resemblance. If experience is to be any guide to us at all—and what scientist can think otherwise, we must conclude that there is only one scientific method: produce a genius and let him do what he likes."

Method is the handmaiden and not the task-mistress of inspiration. Some scientists, like some artists and poets, do not possess the technique necessary to support their inspiration. Conversely no amount of technical skill, however busily applied avails those without inspiration.

The great poet and painter William Blake is an example of both the success and failure of inspiration. If you compare him with poets such as Crabbe & Cowper, both excellent technicians, you know immediately that his gigantic inspiration puts him in a different class from those lesser men. In his painting however although equally inspired, he is not nearly so impressive. His painting seldom has the impact of his poems and is often less satisfying than men whose inspiration was much inferior to his, such as Reynolds and even Canaletto.

We know almost nothing of the source of inspiration, whether this is poetic, artistic or scientific. We know that it usually shows itself before the end of the fourth decade and that it is assumed to have some relationship to what we call intelligence, but it is not assured by intelligence alone.

In science as in war there has been a tendency for the little platoon to outdistance the big battalion. What follows is the story of one little platoon which set out three and a half years ago and has travelled some distance, if not towards its objective, at least from the point where it started.

The Start of the Journey:

You may feel that I am unwilling to spare you even the most trivial details. My reason for this is that if our work is useful an accurate record may help others; and even if it proves useless I shall still have underscored a truth which cannot be emphasized too frequently. Discovery, history shows, treads a hidden path. If this were not so, it would have been found long ago. Nevertheless we usually expect to gain new knowledge by old thinking.

About three and one-half years ago, when I was working under Dr. Desmond Curran at St. George's Hospital in London, England, we were joined by a junior resident, who had transferred from surgery to psychiatry because of an interest in philosophy and parapsychology—subjects so unattractive to members of our speciality that a colleague from another hospital apologized for having introduced the bearer of such unorthodox ideas to our unit. It is good to note this, for we often boggle at people with ideas which seem strange to us forgetting Bishop Creighton's observation that all true knowledge exceeds common sense.

The new arrival was my friend Dr. John Smythies. Shortly after he joined us at St. George's he found an odd volume of the Journal of Mental Science containing Tayleur-Stockings'[57] Gaitskell prize paper on the mescalin phenomena. Smythies recognized that in the present state of knowledge there was no way of accounting for these phenomena. He also found a reference to the use of mescal in divination by certain Indians. To hunt down this reference he secured Rouhier's[52] monograph from the Society for Psychical Research and found in this book the structural formula for mescalin. He thought that it was familiar but could not place it and neither could I. Luckily, a biochemist, Dr. Julian Redmill, then a medical student, was in the building and Smythies asked him. Redmill said that the formula resemble that of adrenalin. We have since discovered that this has been known for years. Many European authors[30,31,40] over the last thirty years had suggested that a toxic substance usually thought to be an amine, might be responsible for schizophrenia, but no one had been lead by this to formulate a hypothesis which would result in searching systematically for such a compound.

At first we thought that an idea so obvious must have been scrutinized and rejected long ago. Smythies made a survey

of the literature and consulted with Dr. Harley Mason,[39] an organic chemist in Cambridge University, England. We decided to pursue our line of thought remembering that "what is now proved was once only imagined."[5] No imagination means no proof. We suggested that in certain circumstances the body produces in addition to or instead of adrenalin, a hallucinogenic, mescalin-like compound which we call M-substance for short.

Sweating It Out:

Inspiration to grow must be watered with sweet. It seems to be equally well nourished by the hot sweat of achievement and the cold sweat of rebuff. Being raw we forgot Milton's warning that: "Truth never comes into the world but as a bastard, to the ignominy of him that brought her forth." If it is truth its essence is unfamiliarity, otherwise it is mere truism.

Our senior colleagues showed a gentle scepticism which saps the spirit more than outright persecution; for that at least forces one to decide whether one's ideas are worth the trouble which they cause.

During 1951 we made several experiments with mescalin which we have reported.[45,46] These simple observations on ourselves and on our friends convinced us that if schizophrenic people have experiences at all similar to mescalin intoxication, but coming on without warning and continuing indefinitely, then, until the aetiology of schizophrenia was known, nothing that might help them should be put aside without testing. The only way to discover these things is to go and see for one's self. It is easy to be smug and ignorant. In the country of the blind, the blind man is king.

In addition to our little experiments we began to develop the rudiments of a method which divides us fairly sharply from most other investigators. I shall discuss this method at some length for since we do not know how to control inspiration, we must at least show proper concern for method.

So let me digress:

Digression:

How do conjurers invent those tricks which delight children and dismay the adults who are asked to explain them?

The conjurer asks a question and the question gives him the ghost of an answer and with that ghost he makes his magic. He asks "What is impossible?" And, once he knows what is impossible, he asks again, "How can I do it?" Then he does it. In this way the conjurer gets inside our guard and we are always deceived.

We believe that we found a question which puts us inside the psychiatrist's guard. This is: "What must be explained?"

In spite of differences between authorities; in spite of the fact that in a recent survey by Altschule[2] this authority stated that there is little evidence of any consistent physiological abnormality of the autonomic nervous system in schizophrenia, the most dramatic disturbances of perceiving, thinking, affect, in consequence of this behavior, do occur. In parenthesis Hoffer's[23] atropine test and Lucy's[38] histamine investigation throw some doubt on Altschule's contention. We must ask ourselves how could such gross psychic abnormalities occur without some changes in the body? My colleague and I postulated that somewhere in the chemical spectrum between adrenalin and mescalin we would find what we were looking for, a hallucinogen with few easily detected, physiological side effects. We had made a hypothesis and the task which lay ahead was to find or build a team which could test it.

Saskatchewan:

I came to Saskatchewan in the fall of 1951 hoping to find someone who would join me in the hunt for the elusive M-substance. In retrospect it seems very unlikely. My colleague stayed in England, trying without success to get support and followed me to Canada a year later. Within 24 hours of my arrival in Saskatchewan I met Dr. Abram Hoffer, the Director of Psychiatric Research, an ideal companion for an adventure of this sort. He saw that if the question which we asked was indeed unanswered, then it was time that an answer was found.

Our question echoed Heinrich Klüver's advice to Hoffer earlier in 1951—to think about mescalin; and spurred on by what he had heard from this famous man, Hoffer started a very extensive literature survey and applied for funds to enable us to start work.

In our attempt to get money we were staunchly supported by Dr. D. G. McKerracher, Director of Psychiatric Services in Saskatchewan and Dr. Charles Roberts of the Department of Health and Welfare in Ottawa.

The clinician and the researcher sometimes ignore the administrator. My friends and I would like to record with gratitude our debt to these two doctors and many members of their departments. Without them our research would have been impossible. The task of distributing research funds is now laid to a large extent on public servants. This is a heavy responsibility, for it is often impossible to distinguish between the crack potted and the original thinker. Indeed it is probably unwise to try and separate these two exactly, for they have a habit of existing side by side, and sometimes inside a single-skin. The public and their elected representatives must accept the hard fact that research is a gamble and that so far we know little about spotting winners. We do know one thing with certainty, and this is, that if you never back your fancy you will never win. We also know that in both racing and research outsiders sometimes come in first.

When one has an hypothesis, things which are usually passed over as bizarre or queer often become a source of fruitful interest. Indeed any one short of ideas need only ask where the adjectives bizarre and queer are frequently used to find something worth investigating. Shortly before I left for Canada, Smythies[55] made a curious observation which linked with others became of crucial importance. In the hope of getting a young and brilliant historian to help us he was asked to listen to a recent mescalin experience of mine. As the recording was played the interest and curiosity which it at first invoked in the historian, was replaced by growing discomfort. At last he said: "I have also had such things happen to me." He then explained that he had suffered from asthma for many years and that during a severe attack he became what he called an "adrenalin addict." Since childhood he had experienced eidetic and hypnagogic imagery but the large doses of adrenalin increased this alarmingly and even when his eyes were open "things looked different."

This suggested that if in some way adrenalin could be deprived of its pressor qualities, it might itself be a hallucinogen. Enquiries among those who take adrenalin medicinally showed that this is not an infrequent happening. Lindeman[37] in 1932 claimed that adrenalin injections aggravated the symptoms of half the schizophrenic patients whom he studied.

We were given another valuable clue by Dr. Asquith of Regina who recollected that during the late war, when it was sometimes necessary to use discoloured adrenalin, larger doses than usual had to be given to get the usual pressor response. This was stopped because of unfavorable reactions, usually psychological disturbances of an alarming sort. No study was made of these reactions, but our attention was drawn to "pink adrenalin."

Hoffer made an extensive survey of what we have named for convenience the hallucinogens—substances which cause profound changes in perception, affect, thinking and behavior, without clouding of consciousness, confusion or gross physiological disturbances. There are very few of them and we know very little about the way they work. All of them can be counted on two hands, even if we include the remarkable amanita muscarin and the mysterious ololuqui. Those whose chemical composition is known will go on one hand. We have fairly reliable information about only five, mescalin, lysergic acid diethyl-amide, hashish, harmine and ibogaine. The active principle of hashish is still disputed. Ibogaine is classified as an indole alkaloid and is known to contain an indole nucleus. You will see from the diagrams that if we assumed that the side chain in mescalin is readily fused with the amino group, which is possible, but not proven, it might be that the indole nucleus is associated with hallucinogenic properties, provided that the compound can pass through the blood brain barrier and is not too toxic. There is one grave objection which you will no doubt have already seen, all these compounds are plant alkaloids and are by definition unlikely to appear in the body.

In April, 1952, armed with this information we met our colleagues of the Departments of Biochemistry and Pharmacology in

the University of Saskatchewan, Professors McArthur, Hutcheon and Woodford. Our grant had just come through.

A month before, Elkes[16] of Birmingham had observed: "to argue from the results of these intoxication experiments to the aetiology of mental disorder is totally unjustified by the available facts" and added later: "knowledge usually depends on method." While it is true that one cannot argue directly from an assortment of exotic vegetable alkaloids to a hypothetical M-substance, it is folly not to concern oneself with these puzzling hallucinogens whose action sometimes resembles schizophrenia so closely that casuistry has been needed to avoid this unwelcome conclusion. Mayer-Gross[41] a very distinguished student of this subject is an excellent example of this determination to avoid the obvious.

"The symptoms of intoxication have been compared with those of schizophrenia. It is much more the strangeness experienced by the patient suffering from schizophrenia and difficulties in describing what is happening in the two conditions which is similar. Many typical schizophrenic symptoms, especially in sub-acute and chronic conditions are never seen in mescal intoxication. Early psychotic phenomena, especially in acute schizophrenia show certain analogues, especially in the field of hallucinations and other sense abnormalities." Surely one cannot expect an unheralded schizophrenic illness, of indefinite duration, in an unprepared victim, and the experiences of a voluntary mescalin taker who knows what to expect and how long the ordeal will last to be exactly similar. What is more remarkable is that the acute reactions have so much in common.[46]

Fischer[17] tells of a prolonged reaction to mescalin which was indistinguishable from an acute schizophrenia. Due to unrecognised liver damage this continued for three days, and toward the end of that time the unhappy subject began to despair and was convinced that he would end his days in a mental hospital. Such happenings are unrepeatable and rarely reported. One would suppose that no one would have the heart to give a hallucinogen to an unprepared person, but it has been done before now and on one occasion the victim of this folly is reputed to have committed suicide.[17]

Very little is known of chronic mescalin taking. I would define this as repeated ingestion of hallucinogenic doses at frequent intervals. Peyote taking by the Indians is apparently reserved for special occasions and the cactus contains a mixture of alkaloids. Fischer[17] has a hearsay account of a man who took mescalin daily for a month to avoid military service in the German Army. He was entirely successful, for he entered a mental hospital at the end of that period and remained there with a severe schizophrenic illness. But who could say whether this was cause or effect?

At our meeting in Saskatoon we raised the question of "pink adrenalin" and suggested that it might be adrenoxyl. Hutcheon pointed out that it certainly contained among other things a substance called adrenochrome.[9,27] In the exciting ten minutes which followed it became clear, as you can see from the diagram, that adrenochrome has a spatial formula related to every hallucinogen whose composition is known. Hutcheon agreed that he and Eade[14] would synthesise this exciting stuff. Following the meeting Hoffer and I drew up a specification for our M-Substance which had eighteen points in it. This had one merit—it could be proved wrong fairly easily.

We still have very little certain information about the "Toxine X" which Jung[31] postulated nearly fifty years ago, or of MacDougall's[40] introverting hormone. True, de Jong[30] and Fischer[18] have made some useful suggestions and there have been other hints from time to time. We have a great deal of negative evidence showing what "Toxine X" cannot be. Unfortunately in the short time which our group has been working it has been impossible to cover a literature which includes more than ten thousand references to schizophrenia and another ten thousand to adrenalin as a start. By failing to do this we have probably missed much that would have been useful. Had we done so we would not have started on our journey yet.

Before discussing briefly some of our research which is now in progress, I shall touch on Agnew and Stefaniuk's[1,56] investigations in the new almost hackneyed field of

mescal and lysergic acid experiences. Accurate information about known hallucinogens is useful in recognizing and constructing new ones, and by experimenting with them we may be able to forge new weapons for the attack on schizophrenia. Much of our present talk of "defences against psychoses" seems to me to be a little short of nonsense. Where one is ignorant of the enemy's disposition defense is certain to fail. Far better to be filled with the spirit of that admiralty standing order which goes, if I remember rightly: "Search, seek out, engage and sink the enemy."

The Model Psychoses

Parallel with our biochemical work we have been experimenting with hallucinogens. Animals are very poor subjects, even in simple matter such as deciding whether they are hallucinating or not, and are useless when one requires subtle and detailed accounts of what they endure. Many humans are almost mute as guinea pigs during the experiments, but luckily they can usually give a detailed report later. It seems to be important when conducting these experiments to be able to accept even the strangest accounts from the subjects. If you are incredulous or unsympathetic, valuable information may be lost.

We hope to be able, before long to show clearly in what way these model psychoses differ from, and in what way they resemble schizophrenia.

We are developing means of modifying model psychoses on the lines of Schueler[53] and Mayer-Gross.[42] An account of one of these modified experiences has recently been reported by Kepner.[33] It is particularly interesting that although Kepner did not have visions or other hallucinatory experiences, some very strange things happened to him which exercised his considerable descriptive capabilities.

There is an odd thing about the literature on mescalin, lysergic acid. In recent years the accounts have become so drab that one might be excused for wondering whether the great hallucinogens had lost their spell over the troubled years. Hoch's[22] subjects are such sad stuff that it doesn't seem as if much happened to them. This failure in communication is probably excused by saying that the experience is already well known. Yet such diverse masters of our craft as Weir Mitchell[43], Havelock Ellis,[15] Mayer-Gross[41], Macdonald Critcheley[10], Heinrich Klüver[35,36] and Beringer[7] are equally struck by the wonder, the beauty, the awefulness and the indescribability of the experience. In my view it is this weirdness, not a growing familiarity or comprehension which has frightened modern investigators away. We like our psychology to be safe and under control, and admission of our huge ignorance hurts us.

In the vaults of a great psychiatric hospital is an account of an artist who under mescalin, hallucinated a three-dimensional, life-sized, tangible, Javanese dancing girl. This lady's claim to hallucinatory status is that, although the artist saw her, touched her and enjoyed her, two psychiatrists who were present say that she was not in fact there. This strange happening was not published because it was considered "too bizarre." Surely there is something bizarre in scientists suppressing observations of enormous interest because they might cause intellectual indigestion and be hard to classify?

In our work we are trying to capture the whole experience and we are still far from doing this. We are not yet well enough equipped in things, people or time. Even so we have already found much of psychological and philosophical interest and we are only scrabbling the surface.

You have lately seen an account in a well known magazine of one of our experiments by a trained observer.[32] I have been told that some people considered this sensational or playing to the gallery. I can assure you that Mr. Katz's account, which in my view is a singularly honest piece of work, is staid compared with Weir Mitchell's. You will later be able to read a report by one of the greatest living masters of English[29] who was good enough to investigate with us.

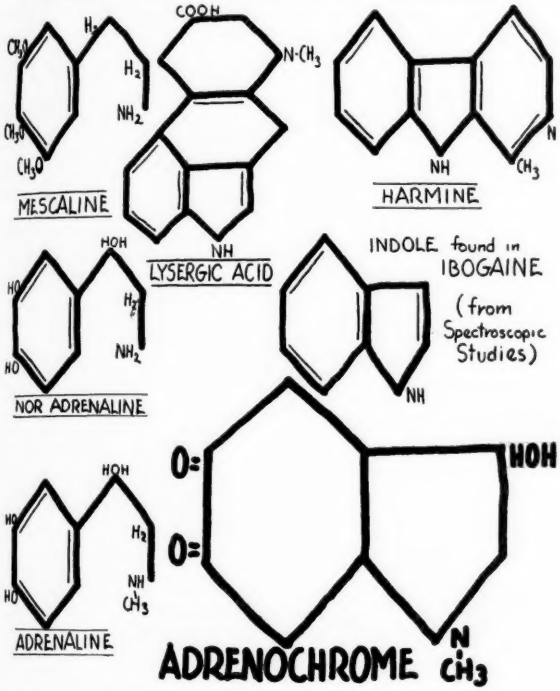
I would urge those who intend to work with the model psychoses to avoid deciding in advance what must or must not happen and to be modest about interpretations of these strange matters. By all means, if you are sceptical go and see for yourselves, but look with unblinkered eyes. Do not be content with such words as "bizarre," "unthinkable," "stupendous" etc. It is our job

as scientists to analyse and explore these labels. If we do not have a suitable vocabulary and other necessary equipment for adventures of this sort, we must seek help from those whose life work is to record the ways of the heart and the soul.

Queen Elizabeth the First, was once advised by a rash ambassador that she must do something. Gloriana replied: "Little man, little man, do not presume to tell great monarchs what they must do." Perhaps we should be as reticent with Great Nature.

TABLE I

Hallucinogenic and Related Compounds



Adrenochrome

To return to adrenochrome, once Hutcheon and Eade[14] had synthesized it and determined its toxicity, we had to test it. It is pretty stuff and when freshly prepared it is a deep purple red, like a cheap port, not tawny enough for a matured wine. I shall not weary you with a long account of its effects which have been described elsewhere.[27] We were lucky enough to have some success with our second subject who had an episode which could have certainly passed as schizophrenic. Since then we have tried several more subjects with differing results. Hoffer and Szatmari[26] have shown that adrenochrome produces interesting changes in the E.E.G. of humans. Woodford[59] has demonstrated on the Warburg apparatus that it is very effective in inhibiting cerebral metabolism. The human brain is fairly sensitive to adrenochrome and this is lucky because our studies on people preceded those on the Warburg. We are continuing our investigations.

The poet, the painter and the composer each learns the technique of his art to master it. Having mastered it he must not be fettered by technique, but must soar to the limits of his inspiration and achieve the highest that is within him. So it is with the scientist, the method is only there to help that nascent flicker of creative energy, which we call inspiration, to achieve its goal.

Summary:

I have then discussed the relationship between inspiration and method in research and illustrated it with an account of a particular research in schizophrenia. Scientific inspiration is as mysterious and hard to define as those springs of musical, artistic or poetic achievement which defy explanation.

Launched and driven by inpiration we steer ourselves by the only compass which we possess, the scientific method. We believe that we have obtained foothold upon a continent whose fringes have often been touched and into whose unknown heart many expeditions have vanished. In the last fifty years scientists have reluctantly become aware that the mind and the soul may not be mere sentimentalities or semantic conundrums. Psychiatrists, in spite of their name find metaphysical questions embarrassing and in bad taste like an oath at a church meeting. Embarrassment must not prevent our recording the truth any more than 19th Century humbug could stop Freud from affirming that sex played a large part in human affairs. Perhaps in ten or fifteen years time we shall have the courage to discuss these unmentionables with as few blushes as we now have for castration fears or incestuous longings.

To return to mundane matters we have found that adrenochrome, a substance which is derived from adrenalin and which could occur in the human body, though its actual occurrence has not been proved, can produce a model psychosis in the human subject, cer-

tain interesting changes in the E.E.G. and inhibits brain metabolism when tested on the Warburg apparatus. Time may show that our hypothetical M-substance does not exist, or that it is a relationship between parasympathetic and sympathetic systems which causes these strange happenings. We are in no position to dogmatize and for those who are sceptical I would prescribe the advice of the immortal Old Bill,[4] "Well, if you knows of a better 'ole, go to it." More seriously, I believe with Francis Bacon,[3] "for though it be wholly rejected, yet that negative is more pregnant of direction than an indefinite, as ashes are more generative than dust."

If in the course of this paper I have made it appear that I think our team has some monopoly of cleverness, let me correct this, now. If we have seen a little further, and this must still be proved, it is because we have the shoulders of men all over the world as a platform. Men such as Gjessing, Klüver, Jung, Hoskins, de Jong, Tayleur-Stockings, Bacq[9] have built well. Professor Quastel is one of the pioneers in the biochemical research in psychiatry, and I do not doubt that everyone is familiar with his classical papers on the action of narcotics on brain respiration,[48] but you may not be aware of his work on faulty liver detoxification, which demonstrated for the first time liver dysfunction in certain acute catatonias.[49] I need not emphasize how deeply indebted we are to him and these other pathfinders. Standing on their shoulders one needs no great stature and only average sight to see some distance ahead.

A clinician, however, must come back to his patients, who are living examples of some of the questions which we are trying to solve. We sometimes mistake their mute agony for indifference and our ears cannot hear the low cry for help which is all that a jangled mind can transmit. To many of them we have little to offer except a sympathy which few possess. Our accounts of their struggles are pallid compared with their own sagas, yet how often do we urge nurses, students and our colleagues to read such classics a "The Witnesses,"[21] "The Exploration of the Inner World,"[8] "The Mind That Found Itself,"[6] "The Kingdom of the Lost"[44] or most terrifying of all descriptions of that inner world, Franz Kafka's great book "The Trial"? The least perceptive after reading these chronicles of gallant struggle cannot fail to approach our patients with greater understanding and must be moved by the challenge of our mighty adversary.

My closing words are those of a nameless sufferer who epitomized in a taut phrase the anguish of tens of thousands of schizophrenic people, "I am enduring," he said, "Trial by Fury."

Author's Acknowledgment: I am indebted to my friends of the Saskatchewan Committee for Schizophrenic Research, Dr. John and Mrs. Elaine Cumming, Professor Heinrich Klüver, Dr. John R. Smythies and Mr. Aldous Huxley for criticism and assistance in writing this paper.

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Doctor-Patient Relationship in Non-Combat Military Psychiatry

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During an informal discussion on psychiatry in the service, while still in civilian practice, General Rawley E. Chambers* warned me against preconceived concepts of military psychiatry as carried over from my civilian psychiatric experience. This paper is the result of observations concerning the therapeutic relationship in military psychiatry made while on active duty with the United States Army.

In the private practice of psychiatry, we permit the development of initial dependency on the therapist by the patient beyond that

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which is necessary for the establishment of rapport. During therapy an attempt is made to examine this dependency and with the development of insight an endeavor is made to relieve the patient of its necessity. In military psychiatry, permitting the development of this dependency is impracticable. Long term psychotherapy in the military service is realistically prohibitive as there is insufficient time for the working through of any transference phenomena that develop. Allowing it to occur in the military patient will often-times preclude any possibility of rehabilitation and return to duty.

Upon first taking over the Neuropsychiatric Ward at Fort Lee, Virginia, in February 1953, there was a census of approximately 20 to 25 patients. (This had been the normal census for the Neuropsychiatric Ward for several years.) Many of these patients had been hospitalized for a period of one month or more. Of this number one was psychotic, one a neurotic-depression, one a severe anxiety reaction, and the rest in that category—emotional immaturity. This last group in civilian life would be recognized as the character disorders and the reactive depressions. The neurotic-depression and the severe anxiety reaction were separated from the service while the psychotic patient was transferred to a Neuropsychiatric Center.

The task remaining was to return the other men to duty. Where feasible this was done immediately, in spite of attempts at cajolery, temper tantrums and suicidal threats. It is obvious that such a move could only be made after more severe psychopathology had been ruled out. In approximately one month the census of the Neuropsychiatric Ward had been reduced to three patients. The census remained two or three patients until June 1953 when it was deemed practical to close the ward entirely. This decrease in census of the Neuropsychiatric Ward was accomplished in spite of the fact that there was no decrease in number or kinds of troops previously in this military reservation. At present the occasional neuropsychiatric case, requiring hospitalization, is kept on an open medical ward and all disturbed cases are transferred to a Neuropsychiatric Center. Approximately 18 cases were transferred during the first six months of 1953. The bulk of the emotional immaturity reactions were sent back to duty and completed training. Several of these patients became chronic visitors to the Post Consultation Service (Mental Hygiene Clinic), and a few of them eventually received administrative discharges for inadaptability. A good number of the previously hospitalized patients went on to do excellent jobs, one becoming an instructor.

The author was transferred to Camp Kilmer, New Jersey, in August 1953, where he worked for several months with Dr. Andrew Ollstein who had been the psychiatrist for approximately two years. In comparing their experiences in military psychiatry, the author and Dr. Ollstein found that they had arrived at essentially the same conclusions, although one served at a Basic and Advanced Training Center (Fort Lee, Virginia), and the other at an Embarkation and Induction and Separation Center (Camp Kilmer, New Jersey). This indicated that their experiences were not unique to a particular kind of installation, but were basically applicable in all military settings. Similar experiences of psychiatric treatment in combat areas have already been reported by Glass and others.[1]

In the U.S. Army Hospital, Camp Kilmer, New Jersey, during January 1952, there were 50 psychiatric in-patients in this 250 bed hospital. In April 1953, it was possible to close the psychiatric ward, just as had been done at Fort Lee, Virginia.

An analysis of the techniques employed revealed that the avoidance of establishing a transference relationship was the most salient factor. It is the job of the psychiatrist to attempt to make a diagnosis during the initial interview as quickly as possible. As soon as disqualifying psychopathology can be ruled out, therapy can be decided upon and disposition of the case made. It is important, wherever possible, to make the diagnosis without resorting to hospitalization. Hospitalization is often resorted to because of the psychiatrist's own anxiety which is usually the result of: 1. inadequate training; 2. emotional insecurity, and 3. failure to recognize the counter-transference and the realistic job of the psychiatrist in the military situation. This occurs to an even greater extent where other medical officers (dispensary

physicians, night duty officers) are concerned. It has been of marked advantage to attempt to orient the other medical officers at the installation concerning the psychiatric aspects of the patients they will see. It is also of benefit to see all psychiatric patients referred for hospitalization before admission, as a large percentage of them may be handled outside the hospital. Following the initial interview, if a patient manifests no disquilafying psychopathology, he is not definitely instructed whether or not he should return. Those who are the "sickest" and are still unable to cope with their situations, return for help by themselves. Of course, the seriously ill are dealt with by immediate transfer to a Neuropsychiatric Center.

The great majority of psychotics and severe symptom neurotics, seen at these facilities, are individuals in whom these conditions existed prior to service. They were in service due to inadequate screening in certain Induction Centers, often in rural areas where trained psychiatric personnel were not available. The author, as a Selective Service psychiatrist, observed that the greatest problem at the Induction Center was to decide whether or not borderline cases of character and behavior patterns should be inducted. Most of these men must be inducted, since their effectiveness can only be determined after an adequate trial of duty. By far, the largest percentage of cases seen are the character neuroses and immaturity reactions, although many of these cases superficially resemble more malignant conditions.

One must start with the premise of avoiding hospitalization wherever possible. This prevents the development of "hospital neuroses," which is as detrimental to rehabilitation of the patient as is establishment of a transference relationship. The enormous secondary gains derived from symptoms developed both on a conscious and unconscious level are extremely difficult to overcome. The distorted incentives precipitated by both situations lead to increased symptomatology and uneconomical behavior.

The less anxiety manifested by the psychiatrist concerning the patient's difficulties, the greater the possibility of returning him to duty. Reinforcing the patient's idea that he is ill must be avoided. This does not necessitate that the doctor be severe or that he exhibit no understanding toward the patient's problem. Reassurance to the patient is not contraindicated in the methods discussed here.

The author learned a great deal from a patient of the passive-dependent type, who was suffering from headaches. This patient had been hospitalized for a month on the Neuropsychiatric Ward at Fort Lee Army Hospital prior to the arrival of the new doctor—the author. During this time the patient had been receiving symptomatic treatment for his headaches. Because he was a college graduate and of superior intelligence, it was felt that he would be a good candidate for intensive psychotherapy. He was seen five times a week, remaining on a convalescent status in the hospital and doing odd jobs, wherever needed. He developed some insight, but would constantly relapse and his headaches would increase to the point of incapacitation whenever the threat of discharge from the hospital would occur. The author became aware of his mistake of joining forces with the patient's already-contrived conscious and unconscious method of "control by dependency," and decided to discharge him from the hospital. The latter had become conspicuous in his continued difficulty in adjusting to the service. When the doctor cut the bonds, the patient constantly attempted to find others upon whom to lean, such as the chaplain, his officers, and the Inspector General. With reassurance from the psychiatrist, these officers refused to become leaning posts, and the patient, in spite of many detours, was eventually able to complete basic training. He was again seen by the author at Camp Kilmer, New Jersey, before he was to go overseas. It was obvious that this patient had never given up his attempts to regain the "control by dependency" that he had once achieved, with the *aid* of the psychiatrist, early in his Army career.

Summary

After two years on active duty as a psychiatrist with the U.S. Army at two military posts, the author has become impressed with the differences of psychiatry in and out of

the service. He has attempted to show that the avoidance of encouraging a transference relationship and the prevention of hospitalization of neuropsychiatric patients wherever possible, are of prime importance in military psychiatry. The author's experience appears similar to that of others, and the lessons learned seem basically applicable in all military settings.

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Complications of Chlorpromazine Treatment

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Chlorpromazine* is a very young member of the family of psychiatric therapies. Even so it is in widespread use throughout the Western World.[1,2,3,4,5,6] The drug has proved effective in a very wide variety of neuropsychiatric conditions. Some have gone so far as to describe the results as miraculous. States of psychomotor agitation and delirium have been notably responsive. Neuroses of all kinds, organic psychoses and convulsive states have been successfully treated in many instances. Most of the available publications, however, indicate that the basic structure of psychoses is untouched by chlorpromazine with delusions and hallucinations persisting unchanged. In the case of schizophrenia the experience of the author suggests the contrary. Almost half of a group of forty paranoid schizophrenics have shown remission of all their symptoms with chlorpromazine and have remained well for up to months. The relapse rate has been very small. The explanation of this difference may be sought in the amounts of chlorpromazine administered. The maximum daily dose cited in the literature is 800 milligrams per day, and is often much less.[3] The largest dosage given by the author has been 3400 milligrams daily. In the series of hospital patients considered below the average maximum dose has been 1400 milligrams. While a healthy respect for the dangers of any new treatment is naturally to be applauded, the recent conclusion of a German author[7] that chlorpromazine is of dubious value is scarcely justified, since he did not give his patients more than four to six hundred milligrams daily.

*Manufactured by Smith, Klein & French Laboratories, under the trade name "Thorazine."

This paper considers the side-effects and complications encountered in 251 cases treated with chlorpromazine. The cases are divided into two groups. Table I shows a summary of the types of patients and results obtained with 67 out-patients. Doses ranged from 30 to 800 milligrams daily, though for the most part did not exceed 150 milligrams per diem. Therapeutic response was judged EXCELLENT where there was total remission of illness or of symptoms interfering with normal life, work and social activities. Where symptoms in general were improved or where presenting symptom was removed the grading is GOOD. A POOR result signifies transient or no relief. The hospital cases

TABLE I

Summary of Results With Outpatients

Dosage rarely exceeded 150 mgms. chlorpromazine daily.

DIAGNOSIS	Therapeutic Results			
	No. of patients	Excellent	Good	Poor
Tension state	24	11	11	2
Anxiety Neurosis	11	7	3	1
Conversion Hysteria	9	6	3	0
Depression—Reactive	2	0	0	2
Migraine	1	0	1	0
Epilepsy	2	1	1	0
Ambulatory Schizophrenia	5	2	2	1
Neurotic and Behavioral Disorders of Childhood	13	8	5	0
TOTAL	67	35	26	6

are listed in Table II. Many, of course, were continued on chlorpromazine after discharge. The dosage range was from 200 to 3400 milligrams per day. Most psychotic patients received a maximum dose of over 1600 milligrams daily. Length of administration varied from as little as 24 hours in some of

TABLE II

Summary of Results With Inpatients

Average dosage 1400 mgms. chlorpromazine daily.

DIAGNOSIS	Number of patients	Therapeutic Response: Remission	Much Improved	Improved	Unchanged
Mania	9	7	2	0	0
Depression	32*	24	1	6	1
Schizophrenia	66	27	22	13	4
Delirium and Confusional States	40	33	3	2	2
Epilepsy	5	2	1	1	1
Narcotic Withdrawal	3	2	1	0	0
Psychotic Episodes in Personality Disorders	4	1	1	1	1
Other	4	2	0	2	0
Neuroses	21	7	9	4	1
TOTAL	184	105	40	29	10

*6 patients received EST in addition.

the delirious patients to nine months in one schizophrenic. This latter patient has taken more than 100,000 milligrams in all! The categories of response in Table II are graded as follows. REMISSION implies disappearance of subjective and objective evidence of mental disease with resumption of normal life. MUCH IMPROVED refers to patients able to live at home and even work, but who still have residual symptoms. IMPROVED includes those whose incapacitating symptoms have been removed but where the basic illness remains in modified form. With the exceptions noted none of these patients were given physical therapy or intensive psychotherapy.

Initial dosage of chlorpromazine in psychotics was nearly always given intramuscularly and changed to the oral form in a few days. Milder cases started out with small oral doses. Effort was made to increase the dosage to therapeutic levels as speedily as possible. A typical course of treatment for a paranoid schizophrenic would be as follows: First day, 200 mg. by injection (divided into four equal doses); second day, 400 mg. by injection; third day, 400 mg. by injection, 200 mg. by mouth; fourth day, 800 mg. by mouth; fifth day, 1200 mg. by mouth and so on until improvement begins. The dosage is then kept constant for one to two weeks and is then progressively reduced to a maintenance level of 200 mg. a day. In some patients this has been continued for months, but the majority do not require it for more than a few weeks. No restrictions are placed on the patient's activities though most are content to stay in bed for the first few days at least.

The complications of chlorpromazine treatment are numerous, though most of them may properly be referred to as side-effects of little consequence. One of them causes no concern to the patient. That is the contact dermatitis occurring in some of the staff who handled chlorpromazine solution. A temporary change of duty seemed to be the only recourse. While the occurrence of a majority of the side-effects was not related either to the size of the dose or the duration of treatment, their intensity often was. Doses of less than 50 mg. per day rarely led to any complaints from the patient. Neurotic patients tended to complain more of side-effects —perhaps because complaining came rather naturally to many of them! It is characteristic of chlorpromazine treatment that the more common side-effects tend to disappear after a few days of treatment. When substantial amounts are given almost all patients are lethargic, sleep a great deal, feel weak, show a minimum of motor activity and feel dizzy for a few days. After this much larger doses are not attended by these discomforts. The clinical picture has been compared with that seen soon after prefrontal lobotomy. The likeness is superficial, since when aroused, chlorpromazinized patients are alert, have no clouding of consciousness and respond readily to questions. Psychological studies have not demonstrated any interference with intellectual functions. The rapid clearing of delirium by chlorpromazine adds weight to these findings.

An attempt has been made to divide the complications into five groups according to etiology, where possible (see Tables III through VII).

Complications Due to Local Irritation:

A burning sensation in the mouth and esophagus was sometimes mentioned by patients at the beginning of treatment and was occasionally associated with a metallic unpleasant taste. It was not persistent.

TABLE III

Complications Due to Local Irritation

	Approximate Frequency %	Significantly Related to Size of Dose
Burning in Mouth and Esophagus	10%	No
Nausea and Vomiting	6%	No
Persistent Bad Taste	2%	No

TABLE IV

Complications Attributable to Autonomic Disturbance

	Approximate Frequency of Occurrence	Significantly Related to Size of Dose
Dry Mouth	90%	No
Nasal Congestion	60%	No
Facial Pallor	40%	Yes
Seborrhea	10%	Yes
Blurring of Vision	15%	Yes
Hypotension	90%	No
Tachycardia	90%	No
Constipation	30%	No
Urinary Frequency	2%	Yes

TABLE V

Complications Attributable to Interference With Central Regulatory Mechanisms

SYMPTOM	Approximate Frequency of Occurrence	Significantly Related to Size of Dose	Persistent
Hypothermia	3%	No	Yes
Fever	18%	Yes	No
Glycosuria	—1%	Yes	No
Increase of Appetite	80%	No	Yes
Respiratory Irregularities	6%	Yes	No
Somnolence	85%	Variable	Rarely
Insomnia	4%	No	No
Inhibition of Drive	67%	Yes	Yes

TABLE VI

Complications Which May Be Regarded As Sensitivity Reactions

	Frequency %	Related to Size of Dose	Related to Duration of Dose	Recurs with 2nd Course
Obstructive Jaundice	0.8%	No	No	No
Dermatitis	12%	No	No	No
Photosensitivity	4%	Yes	Yes	Yes
Arthritis	—1%	Unknown	Unknown	No

TABLE VII

Complications of Unexplained Origin

	Frequency of Occurrence	Related to Size of Dose	Related to Duration of Treatment	Recurs with 2nd Treatment
Alarming Dreams	25%	No	No	Yes
Tremor	16%	Yes	Yes	Yes
Parkinsonism	7%	Yes	Yes	Yes
Confusion	1.5%	Yes	Yes	Unknown
Catatonia	—1%	Yes	Unknown	Unknown
Engorgement of Female Breast. Secretion of Colostrum	12%*	Yes	No	Unknown
Increased Sexual Desire	9%	No	Unknown	Yes

*Of female patients.

Chlorpromazine is used clinically as an antiemetic. The paradoxical nausea and sometimes vomiting which occurred in six per cent of the patients is presumed to be due to local irritation. Procaine tablets given with each dose prevented it.

Complications Attributable to Autonomic Disturbance:

With the exception of the hypotension few of these sides effects caused much concern. The drop in blood pressure followed intramuscular injection within thirty minutes. The systolic decrease was rarely more than 30-60 mm. of mercury, and the diastolic about half that amount. During an intensive course the diastolic pressure went as low as 40 mm. of mercury. The hypotension only bothered the patient during postural changes and he soon learned to change position slowly to avoid dizziness. Fainting has been reported by others. Hypertensive individuals exhibited a much greater drop in blood pressure—often to normotensive levels. The blood pressure slowly returned to pre-treatment levels indicating that chlorpromazine is not an effective hypotensive agent. Sudden withdrawal of the drug was infrequently followed by a sharp rise in blood pressure. Blood pressure was recorded routinely once daily but it has never been found necessary to interrupt treatment on this account.

Nasal congestion also diminished with time. If troublesome, vaso-constrictors were utilized. Blurring of vision due to disturb-

ance of the accommodation mechanism and perhaps also due to dilation of the pupil has been noted in some patients on large doses. Transient constriction of the pupils often occurred at the beginning of treatment. When pallor was marked the patient had quite a striking appearance, and was commented upon adversely by the patient's relatives. There was, of course, a ready remedy for the women patients.

Complications Attributable to Interference With Central Regulatory Mechanisms:

This group of side-effects is not without interest since it may afford clues about the site of action of chlorpromazine. Many of these same symptoms are seen with lesion in the regions of the third ventricle. Reduction of temperature has been mentioned by French authors[1] as a consistent finding. In this series the reverse was true. High fevers —up to 105 degrees—of brief duration were not uncommon with doses over 1000 mg. daily. Often recurrent, they caused the patient little discomfort and were sometimes discovered only on routine temperature checks. There was no associated leucocytosis. Slow or faulty response of the thermal regulating mechanisms to temperature changes did occur. One patient found passing in and out of an air-conditioned office quite a problem. This property of the drug has been put to use in expediting refrigeration before some kinds of surgery.

Increase of appetite was a very desirable feature in many patients. While it led to excessive weight gain, this was rarely permanent. Particularly with depressed patients, increased appetite might precede any other sign of improvement.

Somnolence has already been mentioned. Often marked in the first few days it has persisted in a small number of patients while they were on large doses. Though occasionally associated with some reversal of sleep rhythm, nocturnal sleep was usually much improved. A small number of individuals experienced an increase of insomnia. These patients also became more nervous and otherwise showed a poor response. All were diagnosed as psychoneurotics and had impressive levels of tension prior to treatment.

Inhibition of drive was most prominent in manics and the organically driven children. It is perhaps a compound of central inhibition, sleepiness and general weakness. In hyperkinetic children it occurred, however, in the absence of any other effects. Like the sleepiness it diminished with time. It was severe enough in some that special nursing care was needed to ensure feeding and elimination. On the other hand, restraints could be dispensed with.

Complications Which May Be Regarded As Sensitivity Reactions:

It appears to the author that jaundice has been a much overemphasized danger of chlorpromazine administration. In one reported series, however, it developed in four per cent of patients.[3] In the present group of patients there were two cases. A 45 year old woman being treated for paranoid schizophrenia became jaundiced while on 1600 mg. daily. Serum bilirubin was 3.6 mg. per cent and there were bile pigments in the urine in quantity. She made no complaint. Three days after cessation of chlorpromazine, serum bilirubin was below 1 mg. per cent. After ten days treatment was re-instituted with frequent surveys of hepatic function. Jaundice did not recur. A 48 year old male treated for demerol addiction had a long history of cirrhosis of the liver and chronic alcoholism. He became very jaundiced after one week of treatment and a daily dose of 800 mg. There was biochemical evidence of hepato-cellular damage. Jaundice disappeared two weeks after chlorpromazine was discontinued. Whether chlorpromazine was responsible was never satisfactorily decided. In a series of 33 patients under treatment a liver test battery was performed every fourth day for at least two months. Despite the fact that several patients had a history of liver disease and abnormal test values before treatment hepatic function remained normal throughout. Several cases of jaundice in this area are known to the author. All had received less than 200 mg. daily. The jaundice was of the obstructive type without parenchymatous damage, and cleared within ten days. Liver biopsies showed edematous changes in the cells lining the biliary canaliculi without changes in the parenchyma. The histologi-

cal picture resembled that seen in the allergic skin reactions. It is considered, therefore, that jaundice may well be an expression of individual idiosyncrasy to chlorpromazine.

A wide variety of skin lesions have accompanied chlorpromazine therapy. Related neither to duration of treatment nor dosage they may safely be regarded as allergies. A fine maculopapular rash, often of limited distribution was most common. Widespread macular rashes, giant urticaria and erthema multiforme have also been seen. In one case a giant urticaria led to exfoliation. Papular lesions of the oral mucosa may occur. A 78 year old woman developed localized hypertophic nodules on the fingers. The skin lesions usually itched and sometimes pruritus was noted without a rash. In mild cases the skin cleared in a few days without withdrawal of chlorpromazine. In all cases the rash faded in a few days when the drug was stopped. Antihistamines were useful for relief of irritation. In no case has the rash returned when the patient has been placed back on chlorpromazine. Intense pruritus on exposure to sunlight developed in a few patients on large doses. One patient of this type sustained severe sunburn after a few minutes exposure. Protection from the sun was obligatory until the chlorpromazine level could be reduced, when the problem solved itself.

Two women with a previous history of rheumatoid arthritis experienced a recurrence while on chlorpromazine. The recurrence was not severe and the inflammation slowly receded after the drug was stopped. It is worth mentioning here that another patient with crippling rheumatoid arthritis, under treatment with the drug for a cortisone-induced psychosis did better, in so far as her arthritis was concerned, with chlorpromazine than with cortisone. The psychosis cleared rapidly.

Complications of Unexplained Origin:

Bizarre dreams were commonly mentioned by patients during the first stages of chlorpromazine treatment. This was especially true of those patients who did not become very somnolent in the daytime. The dreams were sometimes of highly charged repressed experiences. In this connection, patients on chlorpromazine, may spontaneously bring forth nuclear conflicts while awake. They do this in a singularly matter-of-fact fashion and are able to discuss them very objectively. A fine tremor was frequently observed in those commencing the treatment but disappeared quickly. Patients on high doses sometimes regained it in the absence of any parkinsonian changes. It was more common in elderly people.

The phenomenon of parkinsonism is perhaps the most intriguing by-product of chlorpromazine. The initial changes associated with chlorpromazine sometimes superficially resembled parkinsonism. However, 17 patients who had been given daily doses in excess of 800 milligrams for over two weeks developed a true parkinsonism. All the patients were under forty and the sex distribution was equal. Five of these became indistinguishable from classical paralysis agitans with masked face, open mouth, dripping saliva, extreme difficulty in articulating and swallowing, cogwheel rigidity of the limbs, pill-rolling movements, coarse tremor and typical posture and gait. In spite of the physican handicap they remained cheerful and mentally alert. Six other patients showed moderate changes (one had extreme rigidity but no tremor) and six more suffered only mild but easily recognizable changes. In about half the 17 cases chlorpromazine was withdrawn and symptoms disappeared in one to ten days. In the other half the quantity of the drug was reduced and at a certain level, which varied for each individual, the parkinsonism slowly disappeared. Very significantly all but two of these patients showed better than average improvement in their original mental condition. Fourteen of them were schizophrenics but it should be noted that most of the patients on very high doses fell into this category. Standard anti-parkinsonian agents had some effect upon the symptoms. One author[8] has reported that chlorpromazine in small doses relieved parkinsonism. Two naturally-occurring cases in this series did not lend confirmation to this, though a child with rheumatic chorea was afforded some benefit.

Four patients on large doses who had earlier shown an improvement in their mental condition, developed a typical toxic-confu-

sional state, after about three weeks of treatment. In three symptoms vanished 24 hours after sharp reduction of dosage. In one schizophrenic male the confusion persisted for 10 days. There were no indications of systemic toxicity and the patients resumed their former progress afterwards.

Catatonia was noted during the second week of treatment in a 24 year old hebephrenic who had previous history of catatonic manifestations. He regained his former hebephrenic picture after two days without chlorpromazine. On returning to chlorpromazine one week later nothing unusual happened.

Dark suspicions were entertained when several of the female patients in the earlier stages of this investigation expressed the belief that they were pregnant. There was engorgement of the breasts with broadening of the areola and a copious secretion. One patient also had changes in the external genitalia. She also said that she felt pregnant, and since she had delivered four children might be presumed to know something about the matter. However, the uterus was small and the frog test negative. These surprising phenomena have been seen in not a few women on high doses. Age is not important. These changes are perhaps related to the increased sexual desire mentioned by both men and women in some instances. A small number of the out-patients have reported an increase in sexual activity but this could well be ascribed to general reduction of tension.

Conclusions:

Chlorpromazine deserves acceptance as a new form of psychiatric treatment.

To be really effective in schizophrenia it must be given in much larger doses than other investigators have considered safe.

There are many complications to chlorpromazine therapy. None appears to be dangerous and all may be managed satisfactorily by reduction of dosage or temporary withdrawal.

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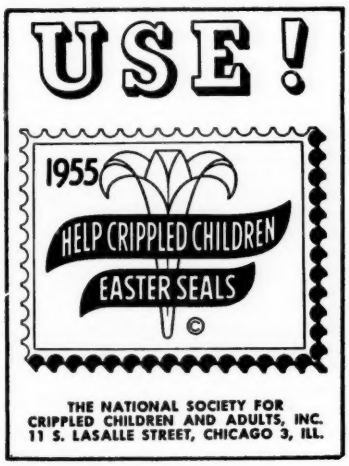

Serial Electroencephalographic Changes Due to Electrotherapy

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Purpose

This study was made to evaluate further electroencephalographic (EEG) changes due to electrotherapy as to type and course. Investigations of a similar nature have been relatively sparse and these have been well reviewed by Chusid and Pacella.[1]

Method

Seriel EEG tracings were made on patients (primarily schizophrenic) taken in chronological order who were given a "standard" course of ECT, consisting of 20 grand mals over an approximate six-week period. Recordings were made with monopolar leads on a six-channel to December 1953, and subsequently on an eight-channel Grass instrument. In order to aid in accuracy, readings were made by two different interpreters using Gibbs et al.[2] classification, and tracings taken at least 24 hours after last treatment. Serial examinations were made before, midway during, and directly after ECT; thence at monthly intervals. An arbitrary time limit of six months post-ECT was later amended to three consecutive monthly normal EEG findings, as experience indicated reversal to the abnormal was quite unlikely.

Since most of the abnormalities consisted of generalized slow waves which varied in intensity, amplitude and frequency, a numerical rating as noted in Table 1, was adopted for ease of evaluation.

TABLE 1

Frequency and Intensity of EEG Abnormalities Rated

Grade	Frequency in Record	— NUMERICAL RATING — Slow Waves S-1	S-2	S-3	Spikes*
Trace (Tr)*	1-4	+	1	2	3
I	5-14	1	2	3	6
II	15-24	4	5	6	9
III	25 +	7	8	9	12

*Note that "trace" and "spikes" are given special weights in ratings due to the relative low and high pathological significance.

The application of the ratings to the raw data is shown in example in Table 2.

From the Veterans Administration Hospital at St. Cloud, Minnesota.

TABLE 2

Sample of Method of Application of Ratings to EEG Abnormalities

CATEGORY		GENERALZED OR FOCAL (F) ABNORMALITIES																			
EEG	*Type*	*Normal*	*Slow Waves*												*Spikes*				*Total*	
	Class*	N	S–1				S–2				S–3				*Paroxysmal*				*Numerical*	
	Rate/sec	8½–12	6–8				4–6				1–3				*Frequency*				*Ratings*	
	Grade	–	Tr	I	II	III	Tr	I	II	III	Tr	I	II	III	Tr	I	II	III	*Slow*	
	Ratings	0	+	1	4	7	1	2	5	8	2	3	6	9	3	6	9	12	*Waves*	*Spikes*
ECT	Before	x																	0	0
	Middle					x			x				x		x				18	3
	End				x				x			x			x				12	3
Months Post-ECT	1				x				x										9	0
	2			x				x											3	0
	3	x																	0	0
	4	x																	0	0
	5	x																	0	0
	6	x																	0	0

*Per Gibbs' Classification.

Scope

The study covered the period from February 1952 to July 1954, and included 167 patients taken consecutively. Of these, 67 were eliminated as they did not fulfill the criteria for a completed series, and the remaining 100 patients served to provide the basic data for the study. The results are noted in Table 3 and Chart 1.

TABLE 3

Number or Per Cent EEG Findings After ECT in 100 Patients

Categories	—*ECT*—			—*Months After ECT*—					
	Before	Middle	End	1	2	3	4	5	6
Normal	98	11	18	85	94	93	50	38	35
Not Done	0	7	1	0	0	0	0	0	0
Ended Series	0	0	0	0	0	5	48	60	63
Abnormal	2	82	81	15	6	2	2	2	2

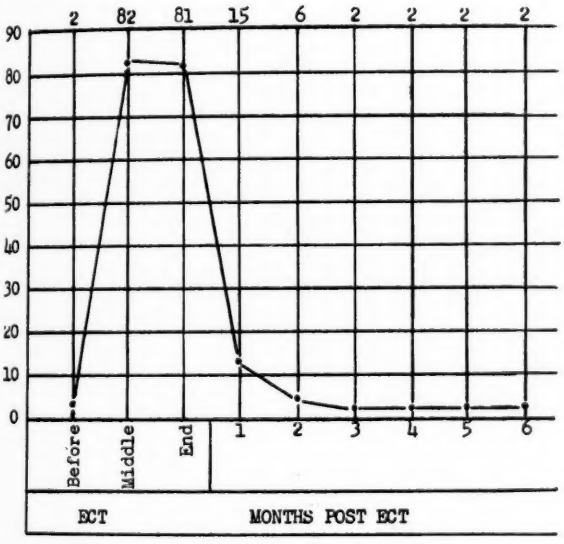

CHART 1. *Graph of Abnormal EEG's with ECT.*

Findings

1. Before treatment, 98% of patients had normal tracings.

2. During treatment, abnormal EEG findings occurred in 82% of patients at midway, and in 81% of the patients at the end of the course of ECT. The type and frequency of the abnormalities were slightly greater (by numerical ratings) at midway, than at the end of the course of ECT.

3. The nature of the abnormalities was generalized slow waves with signs of seizure activity (spikes). The latter occurred occasionally in five patients and severely in one for about two months without clinical seizures. Spikes occurred in one patient in the fifth month post-ECT with clinical seizures persisting for at least one year.

4. Return to normal EEG findings was noted in 98% of the patients (similar to findings before treatment) by third month post-ECT.

5. Five patients ended treatment by the third month post-ECT (see Table 3). These patients had normal EEG's at end of treatment and for each of two consecutive months, fulfilling the criteria for three successive normal EEG's.

6. Due to administrative error, seven tracings midway during, and one at end of ECT course were omitted.

Summary

1. The study included 167 patients receiving a "standard" course of ECT from February 1952 to July 1954. Of these, 100 completed serial EEG studies.

2. Approximately 82% of patients developed abnormal EEG findings after ECT treatment, consisting primarily of generalized slow waves with seizure activity in seven patients. One of the seven had persistent clinical seizures and abnormalities of the EEG for at least one year post-ECT.

3. A return to normal EEG findings was noted in 98% of the patients by the third month post-ECT.

Author's Note: The technical assistance of Gilbert Lommel, EEG Technician, is gratefully acknowledged.

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Use of Serpasil on a Disturbed Ward

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This is a preliminary report on the use of "Serpasil," a pure alkaloid of rauwolfia root introduced by Ciba. It has been extensively used in small doses in the treatment of hypertension. Kline[2] and others, in personal communications, report that "Serpasil" has a tranquilizing effect on disturbed people. While there is insufficient literature on the action, dosage and indications of the drug Nace and Williams,[1] Catlet[3] and Kline indicate that the drug is useful on disturbed patients and our observations definitely confirm that finding. However, much additional research is necessary. What is the minimal, maximal or the optimal dose? The reports of its use on disturbed patients vary in dosage from 2 to 10 mgm. a day. We find that the dosage varies with the patient and type of illness and that large doses are neccessary —but how large?

We plan to learn how much to give, for whom to prescribe, what to expect, how long to prescribe, how will "Serpasil" work; can other medicines be used with "Serpasil," and how we may use the drug to best advantage. These are some of the questions that arose at the start of study and which we are endeavoring to answer.

Patients on acutely disturbed service usually are there because of their hyperactive, assaultive, explosive or unpredictable behavior. In many instances they were refractory to such treatments as psycho-therapy, sedation, shock therapies, and even lobotomies. In some instances family consent for shock therapy could not be obtained. The necessity for treatment of such patients though obvious, is limited in scope and frustrating. True, many such patients burn out their hyperactivity or have a spontaneous remission as reported in controlled studies; but until then they are a challenge. Progress in treatment of the chronically disturbed patients is therefore vitally needed.

Serpasil has been advanced as a non-sleep producing sedative. To test its efficiency, we selected a variety of patients and tried various forms of administration. Some were started orally 5 mgm. daily; others 10 mgm. daily. Some received 5 mgm. by hypo and some received combination of hypo and oral administration. Those receiving 5 or more mgm. by hypo show an improvement in 48 or 72 hours. A mild relapse occurs as they build up resentment against the hypo. Those receiving oral medication have no set time when improvement begins to appear. It varies from one to four weeks.

Patients who have failed to respond to other severe modalities of treatment will naturally put to the test the usefulness of a new treatment. In such patients even a minor improvement is valued. If it makes the patient more accessible to other therapies, then "Serpasil" is of use. The medication was then given to patients who varied in type of illness and who resisted treatment.

The patients studied were selected to provide variation as to age, physical and mental conditions. The youngest was 25 and the oldest 62. In the older group one must be careful of larger doses because of vagal action of "Serpasil." One man, age 56, after one dose of 5 mgm. had sharp a drop in pressure from 115 to 80. Since he was a known coronary he was treated with greater caution. He was kept on 2.5 mgm. and improved clinically.

A group of 15 patients was studied; eight schizophrenics, more or less typical; four post-lobotomy. Two more were disorder personalities who behaved like schizophrenics under stress and were carried as schizophrenics. Two were epileptic, one of whom was post-lobotomy. One was a manic; one was an involutional melancholic (in chronic alcoholism) and one was in severe depression. One was a severe neurotic with psychotic overlay.

There were no toxic reactions except for one patient who is described above. Two patients received medication for three months

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and three patients for two months. One patient received medication for six weeks up to the day of his lobotomy. He had respiratory difficulties during surgery and it was necessary to complete the other side the following week. Subsequently another patient on "Serpasil" was scheduled for lobotomy and his "Serpasil" was discontinued four days prior, with no ensuing respiratory difficulties. This is an observation in only one case and is reported for future use but not for establishing a scientific criterion.

Observations of the patients are recorded in Table I. Patients were graded +1 to +4 to indicate the degree of improvement. Zero means there was no change and +4 means greatest improvement.

TABLE I

	Assaultiveness	Cooperative	Anxiety	Accessible	Delus. or Halluc.	Hostility	Add. Medic.	Length of Medication in Days
1.	+1	0	+1	0	0	0	No	19
2.	+3	+3	+2	0	0	+1	No	50
3.	+1	+1	0	+1	0	+1	No	35
4.	+2	+2	+2	0	0	+1	Yes	21
5.	+3	+2	+3	+3	0 - +1	+3	Yes	64
6.	0	0	0	0	0	+1	Yes	64
7.	+1	+1	+1	0	0	0	Yes	58
8.	+1	+3	+3	+3	+2	+3	Yes	90
9.	+2	+2	0	0	0	0	No	40
10.	+2	+2	+2	0	0	0	No	19
11.	0	+2	+2	0	+1	+1	No	8
12.	+2	+2	+2	0	0	+1	No	17
13.	+1	0	+2	0	0	+1	No	20
14.	+2	+2	+1	+2	0	+1	No	93
15.	+1	0	+1	+1	0	+1	No	19

The patients who had additional medication will be studied further. Patient 4 and 6 are epileptics who received "Dilantin" and phenobarbital during their course of treatment. Patient 4 had fewer seizures, and received 5 mgm. twice a day. Patient 6 had no change in his seizures and received 5 mgm. a day. A month after patient 5 was on "Serpasil" he tried to remove a cast from his hand. He was then placed on a 1/100 of hyoscine and became more cooperative, much less tense and assaultive. Patient 7 was a severe neurotic of seven years' duration with visual and auditory hallucinations and suicidal attempts. At first he was over-enthusiastic about his relief of anxiety, but after 42 days of "Serpasil" treatment he began to demand bedtime medication. It is important to note that at this time both he and his wife seriously discussed lobotomy; and this discussion increased his anxiety. He did receive a lobotomy.

The table shows that such abnormal reactions as assaultiveness, anxiety, hostility, lack of cooperation respond best, and delusions and lack of accessibility, least.

Medication was discontinued on 8-24-54 for the purpose of control study. Within a week the following was observed:

Patient 1—Became more assaultive. Hallucinations appeared more active.
Patient 4—Frequent seizures, more hyperactivity, more restraints.
Patient 5—No change. Maintained on four daily doses of Hyoscine.
Patient 6—Showed no improvement with "Serpasil" and no change after discontinuance. He had received only 5 mgm.
Patient 8—Requested hydrotherapy, became untidy, reacted to auditory hallucinations.
Patient 9—Sustained mild improvement as to assaultiveness.
Patient 10—Hyperactive, hostile, assaultive.
Patient 11—As dose was decreased he returned to religious preoccupation, agitation and abnormal hostile behavior.
Patient 12—Maintained improvement.
Patient 13—More assaultive. Hydrotherapy and sedation of little effect.
Patient 14—Untidy, mute, resistive, catatonic.
Patient 15—More disturbed, more hostile, untidy. In less contact.

Patients 2 and 7 were excluded from this study as they received lobotomies after their course of "Serpasil." Patient 2 was cooperative and pleasant after surgery; patient 7 was hyperactive after surgery. Patient 2 had "Serpasil" to the day of surgery;[2] patient 7 had his "Serpasil" stopped one week before surgery.

Patients 6 and 13 were on 5 mgm. a day and their improvement was slight. Patient 11 (the patient with coronary disease) remained on 5 mgm. When the "Serpasil" was discontinued for the others he was also included, but his agitation became severe, and due to his complicating coronary disease it was decided to treat his agitation. Thus medication was resumed and remission in his symptoms followed.

The table below indicates the reported responses to medication as well as a comparison before and after medication. The first three columns are the responses to medication. The last three are behavior after the medication was stopped.

TABLE II

	EFFECTS OF SERPASIL			SERPASIL DISCONTINUED		
Patients	Materially Improved	Mildly Improved	No Improve.	Severe Relapse	Mild Relapse	No Relapse
1.		X			X	
2.	X			1		
3.		X			X	
4.	X			X		
5.	X					X2
6.			X			X
7.			X	1		
8.	X				X2	
9.		X				X
10.	X			X		
11.	X					X3
12.		X				X
13.		X			X	
14.	X			X		
15.	X			X		

1. Received Lobotomy after "Serpasil" discontinued.
2. Hyoscine had to be used after "Serpasil" discontinued.
3. Continued to receive "Serpasil."

Seven out of fifteen were materially helped and six were mildly helped by the administration of "Serpasil." Abnormal behavior like hyperactivity and assaultiveness were reduced, but more important, there was a change in the emotional status. There was less apprehension, less anxiety, less depression. When there was no improvement in anxiety, there was no improvement in behavior. In some ways this "Serpasil" decrease in anxiety can be compared to post-lobotomy improvement, but in less degree. It does not create the patient's resentment to treatment such as observed in lobotomy, shock, hydrotherapy and sedation.

We have used 5 and 10 mgm. "Serpasil" per day. Thus far we have observed that 5 mgm. is too small a dose for chronically disturbed patients. Ten mgm. will start an improvement, but in some instances that is also too little. Additional study with daily doses of more than 10 mgm. is recommended. We have observed that "Serpasil" is not antagonistic to such commonly used medications as "Dilantin" and barbiturates, but may be considered in effect to be synergistic.

Some patients have had "Serpasil" medication for 2½ months. When it was discontinued they rapidly reverted within a few days to their former behavior and clinical picture. This, then, tends to show that "Serpasil" is not cumulative, that it must be given over a long period of time, and when it is discontinued after clinical improvement, patient must be watched carefully to determine whether improvement will remain without the medication. In two instances, because of assaultiveness and destructiveness, we used hyoscine after "Serpasil" was discontinued and obtained clinical improvement. This latter procedure suggests the possibility that in some refractory patients, "Serpasil" may be combined with hyoscine for greater effect.

One of our patients was a very severe neurotic with strong guilt feelings and severe masochistic and self-punitive behavior, who reacted very favorably when the medication was begun. In fact, he was observed to be over-enthusiastic. After two months he reverted to his demands for sedation. The opinion is expressed that "Serpasil" will be useful only in those neurotics who actually desire symptomatic relief.

In our opinion, "Serpasil" has reached a place of prominence on a therapeutic program for chronically disturbed patients, similar to shock, lobotomy, or hydrotherapy. We found that it can be combined with other medicines and acts synergistically. Medication cannot be stopped abruptly without causing severe relapse and long courses of "Serpasil" therapy are required. Patients vary in response to "Serpasil," but an obvious decrease in anxiety takes place.

Author's Note: The Serpasil used in this study was generously supplied by Ciba Pharmaceutical Products, Summit, N. J.

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Neurological and Neuropathological Conference

(Case No. PM 9559)

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K. M. EARLE, M.D., *Neuropathologist*

Presentation

Patient, Mrs. C.M., age 44, was admitted to the neurosurgical service at the University of Texas on 9/30/53. The history, as given by the patient and her husband, was that of severe headaches and a disturbance in vision. The headaches had begun six months prior to admission. Onset was usually in the occipital region and they progressed over the top of the head and finally involved the entire head. At times there seemed to be more pain on the left than on the right side. The headaches were not related to any particular incident but were said to be increased by coughing or straining. They gradually increased in frequency and severity and would occur at any time during the twenty-four hours, and she would have a free interval between them. There has been no associated nausea or vomiting.

Some six weeks before admission patient noticed that she could not see to her right side and that objects would also seem blurred when looking straight ahead. This visual defect had seemed to increase up until admission. She had even ceased driving her car, as she was fearful that she might have an accident.

The past and personal history indicates that some 15 years before, she had had what was called a "nervous breakdown," from which she made a spontaneous recovery. The description of her symptomatology at that time suggested an endogenous depression. She suffered a fractured nose in a car accident around this period but no history of fainting spells.

General physical examination revealed a blood pressure of 130/80; pulse rate of 80; and respiration, 20/minute. General systemic examination was essentially normal. The only significant neurological finding was a right homonymous congruous hemianopsia. X-rays of chest revealed the heart and lung fields to be within normal limits for her age. Skull films were said to be negative, although the pineal gland was not calcified. E.K.G. was normal. The blood Wassermann was negative and the urinalysis and complete blood count, non-contributory. The spinal fluid revealed 8 white blood cells; 29 mgm.% protein, and a negative Kolmer. The electroencephalogram revealed a normal tracing.

The impression was that of a space occupying lesion in the left temporal, or parieto-occipital region.

The patient was then subjected to further diagnostic studies. A pneumoencephalogram showed poor filling and immediately this was followed by a ventriculogram, which did reveal good filling of the basal cisterns and subarachnoid pathways with no evidence of significant pathology. The ventricles showed a small amount of air which outlined their extent fairly well, revealing no gross displacement or defects. With these negative studies an arteriogram was made, with the dye being injected into the left carotid artery. It showed a normal filling and distribution of this vessel and its intracranial branches, with no roentgen evidence of pathology. Because of the negative findings it was then decided that the hemianopsia was the result of some degenerative lesion.

She was seen in consultation by the neuropsychiatric service. Further history revealed that during the last six months the patient had also experienced a severe sleep disturbance, general nervousness, irritability, loss of appetite, and loss of interest in her surroundings. The story of her headaches changed in that she now said they tended to be persistent rather than periodic. She was moved onto the psychiatric service and within two days had become quite active, and there was a disappearance of all of the above symptoms including her headaches (visual defect persisted). She was discharged from the hospital on 10/24/53.

Subsequent correspondence indicated that she got along reasonably well until about Christmas time. Up until then she was able to do her housework, but thereafter her headaches increased and she began having vomiting spells. The intensity of her headaches, and severity of her vomiting increased, and three weeks before her second admission on 2/6/54, the patient began to show signs of confusion. She is said to have had three fainting spells thereafter. Within the last few days she had become quite confused and would have periods of drowsiness. At the time of re-admission she was showing disorientation, poor memory, irrelevant talk, had a stiffness of her neck, and bilateral papilledema with retinal hemorrhages. Her uncooperative state prevented an accurate visual checkup. She was more confused the following day.

After preparation for surgery, including I.V. fluids, typing and cross matching, a ventriculogram was done in the afternoon of that day. This emergency procedure was deemed advisable after the patient lapsed into coma. The ventriculogram revealed that the third ventricle was displaced toward the right due it was thought to be a space occupying mass in the left fronto-parietal region. A craniotomy performed immediately revealed a bulging tight brain. Internal decompression was performed; bone flap discarded, and closure was made only of soft tissue structures.

The patient remained in coma, running a pulse of 40 to 46/minute until she expired at 7:45 a.m. on 2/8/54.

From University of Texas, Medical Branch, Galveston, Texas.

Clinical Discussion—Dr. Ford:

If one carefully reads the entire abstract prior to dissecting the symptoms and signs as to their chronological development and particular meaning, it seems obvious that the patient had a progressive intracranial lesion of the space occupying variety. Progression is the keynote in this case with the exception of the apparent improvement following the pneumo- and first ventriculogram. This probably was associated with improved intracranial hydrodynamics and with decompression.

This case points up a few lessons. Headache as the first symptom merits attention as the prevalence of chronic headache is well known. Statistics show that only a small per cent (10-20%) of headaches are due to physical causes; while a lesser percentage, estimated around 5% are due to specific intracranial pathology. With percentages in the other direction the clinician may overlook the organic headache unless its characteristics are properly evaluated. Before proceeding, it is equally important to recognize a non-organic headache in order to preclude unnecessary and expensive laboratory studies, further fixation of the headache syndrome, et cetera.

This patient had many of the features of a headache due to altered physiology of intracranial vessels. Her headaches were intermittent; rather than continuous as found in the very common psychogenic (tension) variety. In specific intracranial disorders, increased intracranial tension may be brought on by coughing or stooping, with increase in pain. Location and mode of radiation is not helpful in the differentiation of her type of pain. For example, functional vasodilator headaches, as migraine, are generally throbbing and pulsating. The headache produced by a space occupying mass results from traction on intracranial venous sinuses or arteries, or irritation of the intracranial portions of 5, 9, and 10 cranial nerves, or of the intracranial portion of upper 3 cervical nerve. It may throb, but more often this pain will be of a stabbing and boring character.

The second lesson for the older physician, is that of "forgetting." Formerly we were taught that the triumvirate of headache, vomiting and choked disc was necessary to make a diagnosis of an area occupying lesion. Together they signify only increased intracranial pressure from any cause. Alpers writes that headache alone is present at some time in 88% of brain tumors, vomiting in 65%, choked disc in 75%, but the three combined, in less than 60%. The lack of nausea and vomiting in this patient should not mislead us.

The patient's first localized neurologic complaint occurred six weeks before the first admission, or some four to five months after the onset of headaches. It consisted of inability to see to the right unless the eyes were turned in that direction. Her only positive systemic or neurologic sign was a right homonymous hemianopsia. The clinician should always look for symptoms or signs which point to a specific site of nervous system pathology and, in cases of suspected intracranial tumors, this may help to localize the lesion. This half loss of vision in the temporal field of the right eye and the nasal field of the left eye must be placed proximal to the optic chiasma in either the left optic tract, optic radiation, or occipital lobe. Nothing is said about her handedness, but with most persons being right handed, perhaps her left cerebral hemisphere was also dominant. Hence, the location of the pathology in the left visual pathway must have been as already noted, either the left optic tract or the left occipital lobe; for there was not the aphasia which would be expected from a lesion of either the dominant left temporal or parietal lobes. (Location of optic radiation.) On the other hand, because of the confusion of the second admission a global aphasia from a then massive lesion which by that time had invaded the occipital, parietal, temporal, and frontal, lobes of the left cerebrum, could have been overlooked.

Just a word about pineal gland calcification in routine skull X-rays. It is calcified in 60% of adults, and when shifted to one side or forward or backward in well positioned X-rays, one may suspect that a supratentorial mass produced the shift. Ordinarily, posterior fossa tumors do not alter its position. *Pineal shift is therefore a helpful adjunct to diagnosis and localization.* Unfortunately, this patient did not have pineal

calcification. Too, to further complicate this picture, spinal fluid protein is elevated in active intracranial pathology; but with a low reading of 29 mgms. % protein, in this case, it is not surprising that the clinicians became speculative after finding a normal ventriculogram and a normal left carotid arteriogram.

I would caution against diagnosing a degenerative intracranial lesion in the presence of such definite headaches. Also, why should this 44 year old, otherwise healthy woman with a normal vascular bed, have had such slowly developing localized encephalopathy?

Caution is also to be exercised when making a diagnosis of a functional psychiatric illness merely because physical and laboratory studies prove negative. Another point to remember, especially for the pure psychologically oriented psychiatrist, is that an apparent functional illness may be an early manifestation of an organically induced personality decompensation. There was in this case a previous definite emotional illness (15 years before) indicative of an endogenous depression which showed her personality pattern of reaction to stress.

Upon re-hospitalization approximately 10 to 11 months after the onset of her first headaches, we find that this patient's condition had progressed to the typical picture of increased intracranial pressure; i.e., headaches, vomiting, and papilledema. If chronic meningitis be eliminated, as was apparent from the clinical course and the spinal fluid examination of the first admission, there remains no doubt that a mass exists. A neoplasm is likely; a hematoma unlikely in this case, chiefly because of progressiveness and lack of the usual fluctuations in the overall course, as generally encountered in subdural hematoma.

It comes to deciding whether this is a primary neoplasm of the left cerebral hemisphere, or one of metastatic origin. There is still no evidence of a primary focus, which certainly would have been evident after a period of eleven months. The rapidity of growth is that of very malignant glioma, probably glioblastoma multiforme, although an astrocytoma has to be considered. Before closing, a final useful hint is the absence of convulsive seizures, unless the "fainting spells" in the final stage were "true fits" associated with cerebral irritation and dysrhythmia. Statistics indicate that convulsions are the first symptoms in 18% of brain tumors which are located above the tentorium cerebelli in the anterior and middle cranial fossa. A supratentorial tumor may be suspected when the first seizure begins after age twenty.

KENNETH M. EARLE, M.D.

Pathological Diagnoses:

1. Glioblastoma multiforme, large, left parietal, post-operative (with extension across corpus callosum into right temporo-occipital region).
2. Fungus cerebri (herniation of brain and tumor through surgical defect).
3. Pulmonary edema and congestion (generalized).
4. Atelectasis of lungs (small, focal areas).

Pathological Findings:

The body was that of a white woman appearing about the recorded age of 44 years. The body measured 170 cm. in length and weighed about 150 pounds. The body showed good muscular development and nutrition.

The head was shaved and there was a recent, sutured, elliptical, surgical incision in the left temporo-parietal region. The bone plate beneath this wound was absent and the dura was not sutured. Through this large defect there was marked herniation of brain tissue and reddish brown, hemorrhagic tumor tissue. The herniated area measured 11 x 8 cm. and projected 3 cm. above the brain surface. The herniation (fungus cerebri) was in the region of surgical removal of tumor. The entire brain was markedly swollen, especially on the left and weighed 1500 grams. There was marked deepening of the tentorial groove over the left uncus and evidence of uncal herniation into the tentorial notch. The cerebellar tonsils showed moderate herniation. At the borders of the fungus cerebri there were scattered petechial hemorrhages in the cortex.

Sections of the brain revealed a large mass of reddish brown tumor in the left parietal and occipital lobes with extension across the corpus callosum into the right temporo-occipital lobe. This tumor was hemorrhagic and showed areas of necrosis. The brainstem was compressed and the midline structures were markedly deviated by tumor mass. Tumor tissue was mostly in the supracallosal white matter and corpus callosum, but extended ventrally to involve the posterior part of the thalamus on the left. Microscopically, the tumor had all of the features of a glioblastoma multiforme.

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